IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Jack L. Arbiser		
Serial No.:	09/765,491	Art Unit:	1617
Filed:	January 18, 2001	Examiner:	Jennifer M. Kim
For:	*CURCUMIN AND CURCUMINOID INHIBITION OF ANGIOGENESIS*		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF TO EXAMINER'S ANSWER

Sir:

This is a reply brief to the Examiner's Answer mailed June 15, 2006, in the above-referenced application. **Submitted with this Reply Brief is a Request for Oral Hearing. The Commissioner is hereby authorized to charge $500, the fee for a Request for Oral Hearing for a small entity, to Deposit Account No. 50-3129.** It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The withdrawal of the rejection under 35 U.S.C. 112, first paragraph is appreciated.

The remaining issues on appeal are:

(1) whether claims 4-6 and 17 are definite,

(2) whether claim 17 is novel under 35 U.S.C. §102(e) in view of U.S. Patent No. 6,218,368 to Wirostko ("Wirostko"),

(3) whether claims 4 and 5 are obvious under 35 U.S.C §103(a) over U.S. Patent No. 5,190,918 to Deutch, et al. ("Deutch") in view of U.S. Patent No. 6,482,801 to Brem, et al. ("Brem"),

(4) whether claims 4 and 5 are obvious under 35 U.S.C §103(a) over U.S. Deutch in view of U.S. Patent No. 5,654,312 to Andrulis Jr. et al. ("Andrulis"),

(5) whether claims 4-6 are patentable as required by 35 U.S.C §103(a) over Deutch in view of U.S. Patent No. 5,776,898 to Teicher, et al. ("Teicher"),

(6) whether claims 10-12 and 18 are obvious under 35 U.S.C §103(a) over International Application No. WO 95/18606 by Aggrawal ("Aggrawal"), and

(7) whether claims 10-12 and 19 are obvious under 35 U.S.C §103(a) over Arbiser, et al. (Abstract), *J. Am. Acad. Dermatol.*, 40(6 Pt 1):925-9 (1999) ("Arbiser") in view of Thaloor, et al., Cell Growth & Differentiation, 9:305-12 (1998) ("Thaloor") and further in view of Aggrawal.

(7) ARGUMENT

Appellant affirms the arguments made in the Appeal Brief.

(i) **Definiteness under 35 U.S.C. 112**

The Examiner alleges that claims 4-6 and 17 are not definite for use of the phrase "an effective amount".

The test for indefiniteness is whether those skilled in the art would understand what is claimed when the claim is read in the light of the specification.

Claim 4 recites a method for inhibiting symptoms associated with angiogenesis in the treatment of skin disorders selected from the group consisting of lymphangiogenesis, Sturge-Weber syndrome, verruca vulgaris, tuberous sclerosis, venous ulcers, molluscum contagious, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor wherein the angiogenesis inhibitor is selected from the group consisting of collagenase inhibitors, angiogenic fumagillin derivatives, 2,5-diaryltetrahydrofurans, aminophenylphosphonic acid compounds, 3-substituted oxindole derivatives, thalidomides, penicillamine and IL12 in an amount effective to inhibit angiogenesis.

The remaining claims 5 and 6 are dependent upon claim 4.

Claim 4 requires the angiogenesis inhibitors be in an effective amount to inhibit angiogenesis. All of the angiogenesis inhibitors recited in claim 4 are known and characterized compounds. That they do not possess a common moiety and differ in physical and chemical characteristics is not an issue here, because one of ordinary skill in the art, would be able to arrive at an effective amount of any of the compounds listed in claim 4 that is effective in inhibiting angiogenesis, for the treatment of the disorders listed in claim 4 using only routine experimentation and known, commonly available assays. An effective amount is a common and generally acceptable term for pharmaceutical claims. According to the MPEP <The common phrase "an effective amount" may or may not be indefinite. The proper test is whether or not one

skilled in the art could determine specific values for the amount based on the disclosure. See *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). The phrase "an effective amount . . . for growth stimulation" was held to be definite where the amount was not critical and those skilled in the art would be able to determine from the written disclosure, including the examples, what an effective amount is. The more recent cases have tended to accept a limitation such as "an effective amount" as being definite when read in light of the supporting disclosure and in the absence of any prior art which would give rise to uncertainty about the scope of the claim. In *Ex parte Skuballa*, 12 USPQ2d 1570 (Bd. Pat. App. & Inter. 1989), the Board held that a pharmaceutical composition claim which recited an "effective amount of a compound of claim 1" without stating the function to be achieved was definite, particularly when read in light of the supporting disclosure which provided guidelines as to the intended utilities and how the uses could be effected.

Applicants clearly state the effect to be achieved, and that is inhibition of angiogenesis. Methods for measuring angiogenesis are set forth in the specification in examples 2 and 3 at page 19, line 18 until page 20, lines 3-16, and were known in the art. Therefore, claims 4-6 and 17 are definite.

(ii) Rejection Under 35 U.S.C. § 102

The Examiner alleges that claim17 is anticipated under 35 U.S.C. § 102(e) by U.S. Patent Wirostko.

Claim 17 defines a method for inhibiting skin disorders selected from the group consisting of lymphangiogenesis, Sturge-Weber syndrome, verruca vulgaris, tuberous sclerosis, venuous ulcers, rosacea, eczema, molluscum contagious, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an effective

amount to inhibit angiogenesis of tetracyclines inhibiting collagenase or a sulfated polysaccharide which inhibits angiogenesis.

Wirostko discloses the use of various antibiotics such as tetracycline for the treatment of age-related macular degeneration. Needless to say, macular degeneration involves the retina, not the skin. The dosage, carrier and formulation as a whole suitable for administration to the eye is not going to the be same as that which is suitable for administration to the skin. The disclosure in Wirostko does not enable a skilled artisan to use tetracycline as an angiogenesis inhibitor for the treatment of acne rosacea. For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling". *Paperless Accounting Inc. v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted). Therefore, Wirostko cannot anticipate claim 17.

(iii) Rejections under 35 U.S.C. 103

Claims 4 and 5 are not obvious over Deutch in view of Brem

As discussed above, claim 4 defines a method of inhibiting symptoms associated with angiogenesis in the treatment of skin disorders selected from a group of disorders, comprising administering to an individual in need of treatment an angiogenesis inhibitor selected from the group consisting of collagenase inhibitors, in an amount effective to inhibit angiogenesis. Claim 5 is dependent on claim 4 and recites the added limitation that the angiogenesis inhibitor is applied topically.

Deutch

Deutch discloses peptide fragments and synthetic analogs of thrombospondin, which mimic or inhibit the biological activity of intact thombospondin. Deutch defines

thrombospondin-like activity as any activity that mimics the known biological activities of thrombospondin, and include cell-adhesion promoting activity, cell mitogenic activity, cell chemotactic activities, hemostatic activities, and any activities that derive from these activities such as tumor cell, microbial or parasite metastatic activity, platelet aggregating activity, fibrinolytic activity, and immune modulation. Deutch discloses a list of utilities for the peptides, such as in wound healing, angiogenesis (whatever this means), malaria, cell attachment, complement modulation, and cell attachment promoter. Deutch defines angiogenesis as the ability to inhibit or enhance the formation of blood vessels or lymph vessels. Deutch does not teach one of skill in the art that the peptide would be effective as a pharmaceutical to inhibit angiogenesis.

Brem

Brem states that minocycline is an angiogenesis inhibitor and a collagenase inhibitor.

Deutch in view of Brem

There would be no motivation to combine Deutch with Brem, to arrive at the method claimed by Applicants. As discussed in Jussila and Alito, *Physiol Rev.*, 82:673-700 (2002) (attached in appendix to Appeal Brief), blood and lymphatic vessels develop in a parallel but independent manner, and factors which affect the development of blood vessels do not necessarily affect the development of lymphatic vessels. Thrombospondin is not a known - or claimed - angiogenesis inhibitor. There would have been no motivation for one of ordinary skill in the art reading Brem, to look to the peptides of Deutch, nor if one did so, would there have been a reasonable expectation of success if the peptide were applied to the skin for treatment of one of the named skin disorders. Therefore, claims 4 and 5 are not obvious over Deutch in view of Brem.

Claims 4 and 5 are not obvious over Deutch in view of Andrulis

Andrulis

Andrulis discloses methods of treatment for inflammatory and autoimmune dermatoses which comprise topical and/or systemic administration of a therapeutically-effective amount of thalidomide. In the discussion of the background, Andrulis states that Thalidomide, by inhibiting TNF-alpha production, inhibits angiogenesis, since TNF-alpha stimulates endothelial cell motility in vitro and has strong angiogenic activity *in vivo*.

Deutch in view of Andrulis

Neither Deutch nor Andrulis disclose or suggest the involvement of angiogenesis inhibitors in lymphangiogenesis. Nowhere in Deutch is there disclosed or suggested, that lymphangiogeneis is caused by angiogenesis as asserted by the Examiner on page 7 of the Examiner's Answer. Deutch merely coins the phrase "angiogenesis activity", which they define as the ability to inhibit or enhance the formation of new blood vessels or lymph vessels. Andrulis states that Thalidomide inhibits angiogenesis, which is the formation of blood vessels. Absent any disclosure in Deutch that an agent that inhibits angiogenesis would inhibit lymphangiogenesis, there would be no motivation for a skilled artisan to combine Andrulis (which cites references disclosing that Thalidomide inhibits angiogenesis), with a reasonable expectation of success in treating lymphangiogenesis. Therefore, claims 4 and 5 are not obvious over Deutch in view of Andrulis.

Claims 4-6 are not obvious over Deutch in view of Teicher

Teicher

Teicher discloses a method of treating a tumor in a host by administering a hemoglobin solution and a chemotherapeutic agent to the host. Teicher also suggests the addition of antiangiogenic agents such as TNP-470 (a fumagillin derivative) and minocycline to the cytotoxic agent for administration.

A skilled artisan would not be motivated to combine Teicher with Deutch for the treatment of lymphangiogenesis. There would be no reasonable expectation of success from such a combination. Deutch does not disclose or suggest that anti-angiogenic agents would be useful in treating lymphangiogenesis. A skilled artisan does not consider the disclosures in a reference in isolation. The disclosure in a reference is interpreted in conjunction with what is known in the art. Angiogenesis is distinct from lymphangiogenesis, and absent any disclosure or suggestion in Deutch that antiangiogenic agents would be useful in treating lymphangiogenesis, claims 4-6 are not obvious over Deutch in view of Teicher.

Claims 10-12 and 18 are not obvious over Aggrawal

Claim 10 defines a method to treat symptoms associated with elevated basic fibroblast growth factor in a disorder selected from the group consisting of angiosarcoma, hemangioendothelioma, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Kaposi's sarcoma, psoriasis, and recessive dystrophic epidermolysis bullosa, comprising administering to the individual in need of treatment an effective amount of a pharmaceutical composition comprising a curcuminoid in combination with a pharmaceutically acceptable carrier to inhibit angiogenesis, wherein the carrier is an ointment for topical administration

containing between one-half percent (0.0%) and five percent (5%) pf the curcuminoid or a polymer formulation for implantation.

Aggrawal

Aggrawal discloses the use of curcumin and curcumin analogues at doses from about 1 microgram to about 100 milligram, as an anti-proliferative agent, for the treatment of pathological cell proliferative diseases such as melanomas. Aggrawal does not disclose or suggest the treatment of the disorders claimed by appellant. Aggrawal discloses the use of curcumin as an antiproliferative agent; doses from about 1μg to about 100 mg are effective. The claimed method utilizes curcumin in a topical formulation containing between 0.5 to 5% of the curcuminoid. It is not clear how the disclosure of about 1μg to about 100 mg being effective for inhibition of proliferation (Aggrawal) would make obvious a topical ointment containing 0.5 to 5% curcuminoid effective for inhibition of angiogenesis as asserted by the Examiner. As stated in the MPEP, "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus. *Id.* See also *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); MPEP § 2144.08". Aggrawal discloses a 1000 fold range for curcumin or curcumin analogs for inhibition of proliferation. Aggrawal does not suggest a concentration for curcumin in this very broad range that would be effective in inhibiting angiogenesis, when employed as a topical formulation. It is not enough to just allege that Aggrawal makes obvious the claimed method. As conceded by the Examiner, Aggrawal does not teach the formulation set for the in claim 10. Claims for an invention are not *prima facie* obvious if the primary references do not suggest **all elements** of the claimed invention and do not suggest the modifications that would bring the

primary references into conformity with the application claims. The Examiner has provided no factual analysis supporting the allegation that a person of ordinary skill in the art would be led to modify the composition taught by Aggrawal, with a reasonable expectation of success, to arrive at the composition defined by claim 10. Therefore, claim 10, and claims 12 and 18 dependent thereon, are not obvious over Aggrawal.

Claims 10-12 and 19 are not obvious over Arbiser in view of Thaloor, and further in view of Aggrawal

Arbiser

Arbiser is not prior art to this application since it was published in June 1999. The present application claims priority to June 30, 1999. Furthermore, Arbiser does not describe the administration of curcumin, and therefore does not disclose the formulation used in claim 10. Arbiser (1999) discloses the use of TNP-470 and 2-methoxyestradiol in the treatment of endothelial malignancies such as angiosarcoma and hemagioendothelioma.

In the Examiners Answer, it appears that the Examiner is discussing the subject matter of Arbiser, et al., *Molecular Medicine*, 4(3):191-195 (1998) ("Arbiser 1998"), and not Arbiser 1999. There is no disclosure or suggestion in Arbiser 1998 of the formulation used in claim 10.

Neither Thaloor nor Aggrawal make up for this deficiency. Therefore, claims 10-12 and 19 are not obvious over Arbiser in view of Thaloor, and further in view of Aggrawal.

(8) SUMMARY AND CONCLUSION

The claims are definite. The claims are not anticipated by the prior art. The claims are not obvious over the prior art.

For the foregoing reasons, Appellant submits that claims 4-6, 10-12, and 17-19 are patentable.

Respectfully submitted,

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